American Journal of Medical Genetics (Neuropsychiatric Genetics) 74:7–11 (1997)

Psychiatric Morbidity in the First-Degree Relatives of Schizophrenic Patients

Shashjit Lal Varma,[1*] Azhar Md Zain,[1] and Suarn Singh[2]

[1]*Department of Psychiatry, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia*
[2]*Psychiatry Department, Hospital Kota Bharu, Malaysia*

There is increasing evidence that genetic factors play a role in the etiology of schizophrenic disorders. One thousand eighty-nine first-degree relatives of schizophrenics and 1,137 controls were studied to discover their psychiatric morbidity. Psychiatric morbidity was found in 16.34% of the first-degree relatives (FDR) of schizophrenics (parents, 5.69%; siblings, 7.71%; offspring, 2.94%) as compared to 6.9% in the controls ($P < 0.001$). Schizophrenia was found in 8.3% of the patient group, which was significantly higher (0.2%) as compared to the controls. Schizoid-schizotypal personality disorder was found in 3.03% of FDRs of the schizophrenic group. Depressive disorder was found in 4.4% and 2.1% in the control and patient group, respectively, which was statistically significant. Morbidity risk of schizophrenia was found in 16.97%, 6.22% and 5.79% of schizophrenia, schizoid-schizotypal personality disorder and depressive disorder, respectively, in the FDR of schizophrenic group. *Am. J. Med. Genet. 74:7–11, 1997.*

KEY WORDS: genetics; morbidity risk; family history

INTRODUCTION

There is increasing evidence that some family members of schizophrenics are psychiatrically abnormal and have been given names such as schizoids, schizoid psychopaths, schizoidia or schizophrenia-spectrum illness. Schizophrenia-related personality disorders (schizoid-schizotypal and paranoid) were significantly more common in the first-degree relatives (FDR) of 295 schizophrenic patients than in the relatives of 98 medically ill controls [Kendler et al., 1984]. Coryell & Zimmerman [1988] found scant evidence that the schizophrenics suffered from a heritable illness. Only 1.4% of their relatives received a diagnosis of schizophrenia. Gershon et al. [1988] studied relatives of either schizophrenia or schizo-affective disorder patients, and found that relatives of both types of probands had a higher frequency than control's relatives of broadly defined nonaffective psychosis. Schizoaffective psychosis or acute psychosis (5.0%) and bipolar disorder (2.2%) were noted in relatives of patients with schizophrenia.

Varma and Sharma [1993] reported psychiatric morbidity in 34.78% and 9.2% of FDR of schizophrenics and surgical controls, respectively. They found that schizophrenia, schizoid-schizotypal personality disorder (SSPD), paranoid personality disorder (PPD), and cannabis use disorders were more prevalent in the FDR of schizophrenics and can be used to identify samples with an increased probability of carrying the schizophrenic genotype. Various studies have reported a wide range of abnormalities thought to be related to schizophrenia, such as schizoid [Cadoret 1973; Stephens et al. 1975], SSPD [Baron et al., 1985; Kendler et al., 1984; Frangos et al., 1985; Varma and Sharma, 1993], PPD [Stephens et al., 1975; Kendler et al., 1984; Frangos et al., 1985], reactive, borderline, pseudoneurotic, doubtful schizophrenia, manic depressive psychosis [Rosenthal, 1971], acute delusional psychosis [Weiner, 1985], alcoholism, particularly alcoholic hallucinosis [Stephens et al., 1975], inadequate personality disorder [Kety et al., 1971], antisocial personality and behaviour [Heston and Denney, 1966; Stephens et al., 1975; Silverton, 1988], mental subnormality [Heston, 1966], neurosis and epilepsy [Mitsuda, 1967]. Stephens et al., [1975] proposed the schizophrenia spectrum as: schizophrenia, non-neurotic personality disorders, heavy drinking, other psychoses, neurotic personality disorders, suicide, and neurotic reactions.

There are some reports of low [Abrams and Taylor, 1983] or even zero [Pope et al., 1982] prevalence of schizophrenia in the FDRs. Planansky [1966] found no conclusive evidence to show that schizoid disorders occur more often in the close relatives of schizophrenics than in the general population, in which their frequency is unknown.

There is at present sufficient evidence to suggest that genotypic schizophrenia is a spectrum of phenotypes.

Contract Grant sponsor: Universiti Sains Malaysia, R&D Section; Contract Grant number 3018/93.

*Correspondence to: Dr. S. L. Varma, Consultant Psychiatrist, 92 Cuthberts Road, Alfredton, Ballarat 3350, Victoria, Australia.

Received 25 October 1995; Revised 26 August 1996

The notion of a spectrum of schizophrenia-related disorders has important implications for genetic research in schizophrenia.

Until now, the majority of studies in this area have been reported from the West, except for a few from Asian or ASEAN countries. The present work was conducted with the aim of studying the frequency and pattern of psychiatric morbidity in the FDR of schizophrenic patients and those of controls.

MATERIALS AND METHODS

Sample

The sample of the present study consisted of schizophrenic probands who were drawn from the in- and outpatient sections of the psychiatric departments of the University Hospital, Universiti Sains Malaysia, and General Hospital Kota Bharu, from 1993 to 1995.

Diagnosis

Diagnosis of the probands was made by clinical interviews according to the DSM-III-R criteria [American Psychiatric Association, 1987]. Detailed study of the FDRs (parents, siblings and offspring) was done. The FDRs of the probands were contacted and administered the FH-RDC questionnaires [Andreason et al, 1977]. The questionnaires were completed by interviews with the key informant [Varma and Sharma, 1993] and other available family members. The medical and psychiatric records were also traced for the affected family member, if available. The final diagnosis was made on the pooled sources of information by the psychiatrists.

Family History-RDC

The family data were collected using the family history method. The interview guide for FH-RDC is a semistructured interview schedule for eliciting information regarding psychiatric illness in relatives of index subjects so that they can be diagnosed in accordance with FH-RDC. The FH-RDC were developed to enable research investigators to use a consistent set of criteria for diagnosing psychiatric illness in relatives of index subjects when it is not possible to examine them directly. These criteria have been developed so that, as far as possible, they are similar to those of the Research Diagnostic Criteria [Spitzer et al., 1978], which are used when a subject is directly examined. The differences in the 2 sets of criteria are based on the need to make allowances for the usual inability of informants to supply detailed information about the psychiatric disturbances of another person. The FH-RDC may be completed on the basis of an interview with the index subject himself or an informant who can supply information regarding the relatives of the index subject. The family history method provides information covering all family members. It is not affected by factors that might lead to misestimation of rates by the family study method, such as suicide, other causes of increased mortality, refusals or moves to distant locations. It also provides a relatively quick and simple initial screening concerning familial illness, collected at relatively modest cost. Andreason et al. [1977] explored the extent to which data collected by these two methods were in agreement and results confirm the usefulness of the family history method. Although it has some limitations, such as underreporting, it has respectable sensitivity for major diagnosis [Zimmerman et al. 1988].

The controls were selected from the patients attending the primary health centres, for minor and transient medical problems, as a separate study (Varma et al., 1993, unpublished). Interrater agreement was analysed using Cohen's kappa statistic [Fleiss, 1981]. For practical purposes, a kappa value of 0.4 to 0.75 indicates fair/good agreement. The interrater agreement between the psychiatrists in the present study was good (0.78) for the index cases, while it was 0.75 for the first-degree relatives.

Method

The FDR of the 172 schizophrenics were studied in detail according to the following procedure:

1. The sociodemographic variables and details of the psychiatric history, physical and mental status examination of the relatives were recorded on a semistructured proforma after obtaining their consent. The hospital records of previous hospitalisation and treatment of probands and relatives were also traced, as they provided useful information.
2. Detailed evaluation of the FDR was done in accordance with the Interview Guide for FH-RDC which was completed on the basis of an interview with the "best informant" [Varma and Sharma, 1993].
3. Diagnosis. The diagnosis of sick relatives was made on the basis of the "pooled source" of information obtained from the psychiatric history, medical records and the family history method and according to the FH-RDC [Endicott et al., 1975]. Since FH-RDC includes antisocial personality disorders (APD), the FH-RDC for schizophrenia-related personality disorders [Kendler et al., 1984] was utilised for diagnosing schizoid-schizotypal and PPD. These criteria were derived from DSM-III, which provides lucid criteria for diagnosing personality disorders. In this study, diagnosis was made on the basis of pooled information from various sources as mentioned above because preliminary experience has shown that this would undermine underreporting, which has been considered as a limitation, when the family history method is the sole source of information.

Morbidity risks for psychiatric disorders were computed on the basis of age at onset distribution in the schizophrenic probands and FDR. Age at onset was defined as the earliest age at which the subject met all the necessary criteria for the disorder. For schizophrenia, unspecified functional psychosis, schizoid-schizotypal and PPD, it was 15–39 years and for affective disorder it was 15–59 years. For APD all individuals above the age of 15 years were considered to have completed their age of risk. Our age at onset data were similar to that observed by others [Kendler et al., 1984; Frangos et al., 1985].

Out of the total sample of 1,141 FDR, 52 relatives had to be dropped because of no/meagre information. Thus, 1,089 FDRs (parents, 344; siblings, 572 and off-

spring, 173) were studied in detail. The age at the time of the death of the deceased relatives was accepted for calculating morbidity risks. Chi-square test was used to analyse the data.

RESULTS

The mean age of the patient probands was 27.69, sd 8.39 years. The majority of the probands were between the ages of 16–35 years. The male to female ratio was 51.2% to 48.85% in the experimental group which was matched with the control group. Almost all (93.8%) of the probands were from rural areas. The mean age of patients' FDR was 30.25, sd 17.54 years. The patients' FDR and controls did not differ-significantly with regard to sex, domicile and marital status.

Psychiatric morbidity was observed in 16.34% and 6.9% of FDR of patients and controls, respectively, which was statistically significant ($P < 0.001$). The percentage distributions of the parents, siblings and offspring were 5.69%, 7.71% and 2.94%, respectively. The prevalence of psychiatric morbidity was observed to be higher in siblings as compared to the parents of patients' FDR. The prevalence of psychiatric morbidity was also lower in the offspring as compared to parents and siblings in both the groups of FDR. However, all these differences were found to be statistically non-significant (Table I).

The pattern of psychiatric morbidity in FDR of schizophrenic and controls is shown in Table II. The depressive disorder group includes depressive disorder and recurrent unipolar, and the bipolar disorder group includes bipolar and manic disorder. Schizophrenia, SSPD, depressive disorder, neurotic disorder were observed to be the most prevalent among the relatives of probands. Schizophrenia and neurotic disorder were found to be significantly higher in the patients' FDR as compared to the controls, while depressive disorder was found to be significantly more frequently in the controls compared to the patients' FDR. Although some APD and bipolar disorder was found in the patients' FDR, no conclusions can be drawn because the number of patients in both these groups was too small and the disorders were not found in the controls (Table II).

The morbidity risks (MR) for schizophrenia, SSPD, depressive disorder and PPD were found to be higher in the patients' relatives. Psychiatric morbidity in the different categories of relatives was analysed. Psychiatric morbidity in parents of probands was 18.02% (62/344). The morbidity risks for schizophrenia, SSPD and the morbidity risk for depressive disorders were higher in the parents of schizophrenic patients. The MR for schizophrenia, SSPD and depressive disorder were higher in the siblings of schizophrenics. The overall psychiatric morbidity among the siblings was found to be 14.68% (84/572). The prevalence and morbidity risk rates for all psychiatric disorders were generally higher in offspring of schizophrenic patients. The overall psychiatric morbidity in the offspring was found to be 18.50% (32/173) (Table III).

DISCUSSION

The present study investigated psychiatric morbidity in the FDR of schizophrenic probands. It employed prospective proband selection, patient and family interviews by semistructured schedules, and diagnosis based on pooled sources of information.

Psychiatric morbidity was observed in 16.4% of FDR of patients as compared to 6.9% in controls. The prevalence rates for psychiatric disorders in patients' FDR was less as compared to the rates observed by other authors [(34.8%, Kendler et al., 1985); (35.5%, Stephens et al., 1975); and (34.8%, Varma and Sharma, 1993)]. However, it was comparable to the prevalence rate (24.6%) reported by Frangos et al. [1985]. Baron et al. [1985] observed psychiatric illness in 59.6% of FDR of chronic schizophrenia. This exceptionally high rate may be attributed to the special features of the sample per se. Firstly, these authors selected chronic schizophrenics diagnosed according to the RDC, with age at onset (21.3, sd 6.9 years) lower than that reported in most other recent series [Baron et al., 1983], which suggests that the patients represented a severe type of schizophrenia. Secondly, there was a marked degree of assortative mating for schizotypal personality disorders among parents in their sample, which points to a considerable genetic input from both paternal and maternal branches of the families studied.

The prevalence of psychiatric morbidity of 6.9% in controls is considerably lower than that reported by other workers [23.1%, Stephens et al., 1975]; 14.3%,

TABLE I. Psychiatric Morbidity in Probands' FDR and Controls

	Patients' FDR		Controls	
	N (n = 1,089)	%	N (n = 1,137)	%
Healthy	911	83.66	1,059	93.1
Sick	178	16.34	78	6.9
Sick FDR Categories				
Parents (344)	62	5.69		
Siblings (572)	84	7.71		
Offspring (173)	32	2.94		
Total 1,089	178	16.34		
Patients vs. controls	$\chi^2 = 49.2$; $P < 0.0001$		Parents vs. siblings	$\chi^2 = 1.79$; P = NS
Siblings vs. offspring	$\chi^2 = 1.05$; P = NS		Parents vs. offspring	$\chi^2 = 0.02$; P = NS

TABLE II. Morbidity Risk of Psychiatric Disorders in the FDR of Patients

	Patients' FDR				Control
Psychiatric morbidity	N	(%)	BZ	(MR)	N (%)
Schizophrenia	90	(8.3)	530.5	(16.97)	2 (0.2)*
Schizoid-schizotypal personality disorder	33	(3.0)	530.5	(6.22)	0*
Depressive disorder	23	(2.1)	397.5	(5.79)	50 (4.4)*
Bipolar disorder	7	(0.6)	397.5	(1.76)	0
Paranoid personality disorder	3	(0.3)	530.5	(0.56)	0
Antisocial personality disorder	5	(0.5)	530.5	(0.90)	0
Neurotic disorder	13	(1.2)	530.5	(2.50)	14 (1.3)
Others	4	(0.4)	530.5	(0.80)	12 (1.1)
	178 (16.34)				1137 (6.9)

*$P < 0.001$ (patients FDR prevalence vs. controls).
BZ, bezugsziffern

Kendler et al., 1985; 18.3%, Frangos et al., 1985 and 27.3%, (Baron et al., 1985). The discrepancy in the prevalence of psychiatric disorders in controls relatives is understandable. Varma and Sharma, [1993], in a study from Asia reported a prevalence of 9.2% psychiatric morbidity in controls, which is near to our findings of 6.9%. One of the reasons may be that in Asian culture the acceptance and reporting of psychiatric problems may be less, due to several factors, one of which is taboo associated with psychiatric illnesses.

The prevalence of psychiatric morbidity was observed to be significantly higher in the parents, siblings and offspring of schizophrenics as compared to the control groups. In both schizophrenic and control groups, a significantly higher prevalence rate of psychiatric morbidity was observed in parents and siblings, as compared to offspring. This is understandable, as a sizeable proportion of the offspring in the group were younger (age ranging from 1 to 15 years) and had not even entered the risk period for psychiatric disorders.

The risks for SSPD, chronic schizophrenia and PPD were significantly higher in the schizophrenic FDR as compared to the controls. The data support the familial nature of schizophrenia. Despite the different morbidity risks reported for schizophrenia, most investigators concur on the familial aggregation of schizophrenia [Stephen et al., 1975; Kendler et al., 1984; 1985; Baron et al., 1985; Varma and Sharma, 1993]. Recent claims that cast doubt on the familial nature of schizophrenia are noteworthy, Pope et al. [1982] observed zero prevalence of schizophrenia among the FDR of schizophrenics and concluded that there is little or no heritability in DSM-III schizophrenia. Abrams and Taylor [1983], using their own diagnostic system, reported 1.6% morbidity risk for schizophrenia in FDR of schizophrenic patients and concluded that the case for familial transmission of narrowly defined schizophrenia is weak. However, both these studies were criticised on methodological grounds [Kety, 1983; Kendler, 1983; Weissman et al., 1983].

Lower prevalence for depressive disorder (bipolar disorder included) was observed in the FDR of patients compared to controls. This is in contrast to the study of Varma and Sharma, [1993], who found a higher prevalence of affective disorder in the schizophrenic families. However, when we compared the morbidity risk, it was 5.79%, which was comparable to other studies. The study of Winokur et al. [1972] also used the same methodology as that in the present study, (i.e., family history method) and found that the parents and siblings of schizophrenic probands had a morbidity risk of about 5.50%. However, there were no controls. The study by Gershon et al. [1988], observed significantly higher MR for affective disorder, particularly unipolar disorder, 16% vs. 7.3% (patients' FDR Vs controls' FDR). The controls of this study, however, were normal volunteers obtained through advertisements and as such, are not comparable to the hospital-based volunteer controls [Tsuang et al., 1980; Kendler et al., 1984, 1985] or acquaintances of well siblings of schizophrenic probands [Baron et al., 1985] of previous studies.

Antisocial personality disorder, bipolar disorder and mental retardation were observed to be more common in the FDR of patients as compared to the FDR of controls. However, since the number of patients in these categories was small, the findings can be considered to be only tentative. Thus, it is apparent that the risk of developing psychiatric morbidity in the FDRs of schizophrenics is quite high and that SSPD seems to be biologically related to schizophrenia and within the boundaries of the schizophrenic spectrum disorders.

ACKNOWLEDGMENTS

We thank the R & D section of the Universiti Sains Malaysia for the permission and funding of this project (Grant 3018/93).

TABLE III. Morbidity Risk in the FDRs of Schizophrenic Patients (n = 1,089)

	Parents			Siblings			Offspring		
Psychiatric disorder	N	BZ	MR	N	BZ	MR	N	BZ	MR
Schizophrenia	26	530.5	4.90	46	530.5	8.67	18	530.5	3.39
SSPD	12	530.5	2.26	21	530.5	3.96	0		
Depressive disorder	12	397.5	3.01	6	397.5	1.50	5	397.5	1.26
Bipolar disorder	3	397.5	0.75	2	397.5	0.50	2	397.5	0.50
PPD	1	530.5	0.19	2	530.5	0.37	0		
APD	0			4	530.5	0.75	1	530.5	0.19
Neurotic disorder	8	530.5	1.50	3	530.5	0.57	2	530.5	0.37
Others	0			0			4	530.5	0.75
	62			84			32		

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